Is There a Role for Tamsulosin in the Treatment of Distal Ureteral Stones of 7mm or Less? Results of a Randomised, Double-Blind, Placebo-Controlled Trial

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Abstract: BACKGROUND: Numerous randomised trials have confirmed the efficacy of medical expulsive therapy with tamsulosin in patients with distal ureteral stones; however, to date, no randomised, double-blind, placebo-controlled trials have been performed. OBJECTIVE: The objective of this trial was to evaluate the efficacy of medical expulsive therapy with tamsulosin in a randomised, double-blind, placebo-controlled setting. DESIGN, SETTING, AND PARTICIPANTS: Patients presenting with single distal ureteral stones </=7mm were included in this trial. INTERVENTION: Patients were randomised in a double-blind fashion to receive either tamsulosin or placebo for 21 d. The medication was discontinued after either stone expulsion or intervention. Abdominal computed tomography was performed to assess the initial and final stone status. MEASUREMENTS AND LIMITATIONS: The primary end point was the stone expulsion rate. Secondary end points were time to stone passage, the amount of analgesic required, the maximum daily pain score, safety of the therapy, and the intervention rate. RESULTS: Ten of 100 randomised patients were excluded from the analysis. No statistically significant differences in patient characteristics and stone size (median: 4.1mm [tamsulosin arm] vs 3.8mm [placebo arm], p=0.3) were found between the two treatment arms. The stone expulsion rate was not significantly different between the tamsulosin arm (86.7%) and the placebo arm (88.9%; p=1.0). Median time to stone passage was 7 d in the tamsulosin arm and 10 d in the placebo arm (log-rank test, p=0.36). Patients in the tamsulosin arm required significantly fewer analgesics than patients in the placebo arm (median: 3 vs 7, p=0.011). A caveat is that the exact time of stone passage was missing for 29 patients. CONCLUSIONS: Tamsulosin treatment does not improve the stone expulsion rate in patients with distal ureteral stones </=7mm. Nevertheless, patients may benefit from a supportive analgesic effect. CLINICALTRIALS.GOV: NCT00831701.

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Is there a role for tamsulosin in the treatment of distal ureteral stones ≤7mm? Results of a randomised, double-blind, placebo-controlled trial

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Abstract

Background

Numerous randomised trials have confirmed the efficacy of medical expulsive therapy with tamsulosin in patients with distal ureteral stones. However, to date, no randomised, double-blind, placebo-controlled trials have been performed.

Objective

The objective of this trial was to evaluate the efficacy of medical expulsive therapy with tamsulosin in a randomised, double-blind, placebo-controlled setting.

Design, Setting, and Participants

Patients presenting with single distal ureteral stones ≤7mm were included in this trial.

Intervention

Patients were randomised in a double-blind fashion to receive either tamsulosin or placebo for 21 days. The medication was discontinued either after stone expulsion or intervention. Abdominal computed tomography was performed to assess the initial and final stone status.

Measurements

The primary endpoint was the stone expulsion rate. Secondary endpoints were time to stone passage, the amount of analgesics required, the maximum daily pain-score, safety of the therapy and the intervention rate.

Results and Limitations

Ten out of 100 randomised patients were excluded from the analysis. No statistically significant differences were found between the two treatment arms in patient characteristics and stone size (median 4.1mm (tamsulosin arm) vs. 3.8mm (placebo arm), p=0.3). The stone expulsion rate was not significantly different between the tamsulosin arm (86.7%) and placebo arm (88.9%; p=1.0). Median time to stone passage was 7 days in the tamsulosin arm and 10 days in the placebo arm (logrank p=0.36). Patients in the tamsulosin arm required significantly less analgesics than patients in the placebo arm (median 3 vs. 7 analgesics,

p=0.011). A caveat is that the exact time of stone passage was missing in 29 patients.

Conclusions

Tamsulosin treatment does not improve the stone expulsion rate in patients with distal ureteral stones ≤7mm. Nevertheless, patients may benefit from a supportive analgesic effect.

Clinicaltrials.gov #: NCT00831701

Introduction

Current therapeutic options for ureteral stones include active intervention as well as conservative "watch and wait" approaches. Endoscopic treatment of ureteral stones has a high success rate and reliably results in immediate stone removal [1, 2]. However, surgical as well as anaesthetic risks are not negligible and serious complications, albeit rare, are possible [3]. Thus, for many patients, a conservative treatment without invasive procedures is an appealing option. Watchful waiting, however, not always results in stone clearance and may be associated with recurrent renal colic [4]. Once a conservative approach proves unsuccessful, interventional treatment becomes necessary. After a period of conservative treatment this is often inefficient or has a higher risk for complications due to stone impaction and the associated inflammatory reaction of the ureter [5, 6].

The therapeutic potential of alpha-blockers for ureteral stone disease has been investigated prompted by the detection of alpha-receptors in ureteral smooth muscle cells [7]. Successful medical expulsive therapy (MET) for patients with distal ureteral stones using the non-selective alpha-blocker doxazosine was first reported in the late 1990's [8]. Since then, numerous clinical trials were performed to investigate the efficacy of MET using the 1a/d selective alpha-blocker tamsulosin alone and in combination with other drugs like corticosteroids and antibiotics [9-18]. Most of these studies were randomised and revealed that tamsulosin treatment significantly improves the expulsion rate of medium-sized (3-10mm) distal ureteral stones. Thus, tamsulosin represents a non-invasive and cost-effective alternative to interventional approaches [19]. However, none of the studies were performed in a double-blind, placebo-controlled fashion.

The objective of this trial was to evaluate the efficacy of MET with tamsulosin for ureteral stones ≤7mm in a randomised, double-blind, placebo-controlled setting.

Material and Methods

Participants: This randomised, double-blind, placebo-controlled trial was performed in the Department of Urology, University Hospital of Zürich with subjects in an outpatient setting. All male and female patients 18 years or older presenting with acute renal colic were evaluated for study participation. Patients with a single ureteral stone ≤7mm below the common iliac vessels, as assessed on non-contrast-enhanced abdominal computed tomography (CT), were eligible for the study. Exclusion criteria were the presence of multiple ureteral stones, renal insufficiency (estimated glomerular filtration rate below 60 ml/min/1.73m^2), urinary tract infection, a solitary kidney or pregnancy. Patients with a history of ureteral surgery or previous endoscopic procedures, hypersensitivity to tamsulosin or current alpha-blocker, calcium-antagonist or corticosteroid medication were also excluded. Patient enrolment was performed by the attending urologist.

Study design: Enrolled patients underwent randomisation in a 1:1 fashion in blocks of 10 to receive either a daily single-dose of tamsulosin (0.4 mg) or placebo. The sequence of randomisation was computer-generated and performed by the university hospital pharmacy using DatInf Randlist software version 1.0 (DatInf GmbH, Tübingen, D). Randomisation data were kept strictly confidential in sealed envelopes, accessible only to the primary and senior investigator. Tamsulosin and placebo were provided by the university hospital pharmacy as gelatine capsules of identical appearance and taste and were presented in identical bottles. Neither the patient nor the attending urologist nor the investigators were aware of study arm assignments until final assessment of outcome.

Sample size calculation was performed based on previous reports of spontaneous stone expulsion and assuming a clinically relevant difference in expulsion rate of 25% [13, 16, 17, 20]. The stone expulsion rate was estimated to be 90% and 65% for patients with and without tamsulosin medication, respectively. A two group chi-square test with a 0.05 two-sided significance level will have 80% power to detect the difference between a group 1 proportion

of 0.65 and a group 2 proportion of 0.90 when the sample size in each group is 43. Fifty patients per group were finally randomised which allowed for a maximum drop-out rate of 14%.

The study protocol was approved by the local ethics committee and the study was performed in accordance with the Declaration of Helsinki. All enrolled patients provided written informed consent.

Intervention: Patients were requested to take the study medication once at the same time each day and to strain their urine. Furthermore, they kept a diary to record the required amount of analgesics, the score of every painful episode on a 10 cm visual analogue scale, the date and time of stone passage and the presence and type of side effects thought to be related to the medication. The study medication was discontinued either after spontaneous stone expulsion, intervention or at the end of the study (i.e. after day 21). After initial analgesia for acute pain management, no regular analgesic medication was maintained. Oral diclophenac (up to 3x50mg) as first-line and oral metamizole (up to 4x1g) as second-line on-demand analgesics were prescribed.

Follow-up was performed weekly with urinalysis, serum creatinine measurement, abdominal ultrasonography and, in radiopaque stones, plain abdominal x-ray. Low-dose abdominal CT was performed to assess the stone status at the end of the study without knowing the treatment allocation. For patients with a stone-free ureter on final abdominal CT but unnoticed stone expulsion, the date of last positive stone status was recorded. Absence of stone expulsion after day 21 was considered as failed therapy. In these cases, either continued watchful waiting or ureterorenoscopy (URS) or extracorporeal shock-wave lithotripsy (ESWL) was performed. Discontinuation of study medication and intervention before the end of the study due to uncontrollable pain, adverse events, urinary tract infections, acute renal failure or the patient's desire for stone removal were also considered as failed therapy. These patients were included in the final analysis on an intention to treat basis. Patients who

experienced stone expulsion before first medication, who withdrew their consent or were lost to follow-up, were excluded from the analysis.

Endpoints: The primary endpoint was the proportion of patients experiencing stone expulsion until day 21, as confirmed by low dose abdominal CT. Secondary endpoints were time to stone passage, the required total amount of analgesics and the reported maximum daily pain-score until stone expulsion, the intervention rate as well as the safety of the therapy. Additionally, factors influencing these endpoints were assessed.

Statistical analysis: Statistical analysis was performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria). Fisher's exact test was used to compare nominal and Mann-Whitney U-test to compare continuous variables between the two treatment arms. Kaplan-Meier estimates were computed for time to stone passage, and compared between the two treatment arms using logrank test. Patients who were able to define the time of stone expulsion were considered events for time to stone passage. Patients with unnoticed stone expulsion were censored at the date of last positive stone status and those who discontinued the therapy were censored at the date of last medication intake. Patients without stone expulsion were censored at day 21. A multiple Cox proportional hazards regression model was generated to assess the predictive value of stone size and location and the prognostic value of therapy, jointly. The significance level in the test for the primary endpoint was set to 0.05. In the exploratory analysis of the secondary endpoints all p-values smaller than 0.05 were considered significant and no correction for multiple testing was performed.

Results

From September 2006 to September 2008 a total of 100 patients were randomly assigned to the two treatment arms. Overall, 10 patients were excluded from the final analysis (Figure 1).

194 In 8 cases, treatment was discontinued due to adverse events or uncontrollable pain with
195 subsequent intervention (URS or ESWL).
196 No statistically significant differences were found between the two treatment arms in age,
197 gender, stone size and stone location (Table 1). Median stone size in the entire population
198 was 3.9mm (interquartile range (IQR) 3.5-4.8mm).
199 The spontaneous stone expulsion rate within 21 days was not significantly different between
200 the tamsulosin arm (86.7%) and placebo arm (88.9%; p=1.0). Univariate analyses revealed
201 that neither patients' gender and age nor left/right location of the stone were predictive
202 factors for stone expulsion. The stone location in the ureter however had a predictive impact
203 on the stone expulsion rate. The spontaneous expulsion of stones at the ureterovesical
204 junction was significantly higher than of stones in the distal part of the ureter (p=0.006). All
205 11 stones which did not pass spontaneously or required treatment before the end of the study
206 were located in the distal part of the ureter. Furthermore, stone size was significantly smaller
207 in the group of patients with spontaneous stone expulsion (p=0.039). The stone expulsion rate
208 was significantly higher for patients with stones of 5mm or smaller compared to patients with
209 stones larger than 5mm (p=0.048). However, the expulsion rate was not significantly
210 different between the treatment arms, neither for patients with stones of 5mm or smaller
211 (p=1.00) nor for those seen with larger stones (p=1.00).
212 The Kaplan Meier estimates for time to stone passage are shown in Figure 2. A total of 50
213 patients (56%) were able to define the time of stone expulsion by collecting the stone after
214 urine filtration. Twenty-nine patients (32%) had unnoticed stone expulsion, 8 patients (9%)
215 discontinued the therapy and 3 patients (3%) were not stone-free at the end of the study.
216 Median time to stone passage was 7 days (95% CI: 4-13) for patients overall and 7 days
217 (95% CI: 3-10) in the tamsulosin arm and 10 days (95% CI: 3-20) in the placebo arm. The
218 difference between the treatment arms was non-significant (logrank p=0.36). A multiple Cox
219 regression model to analyse predictive factors for time to stone passage revealed only stone

location but not medical therapy or stone size as predictive factors (Table 2). The hazard of expulsion at any time was 3.0-fold higher for stones located at the ureterovesical junction than in the distal part of the ureter.

The required total amount of analgesics until stone expulsion was significantly different between the two treatment arms (p=0.012). Patients in the tamsulosin arm consumed a median number of 3 (IQR 1-9.8) and patients in the placebo arm a median number of 7 analgesics (IQR 4-16) until stone expulsion. Figure 3 shows the course of the medians of the most painful episodes per day. Only the first 10 days were analysed due to the low number of patients being at risk after that day.

No severe complications were recorded. Hospital re-admissions with consecutive intervention and discontinuation of the medication were due to uncontrollable pain (7 patients) or side effects (1 patient). Six patients (13.3%) in the tamsulosin arm (URS: 4, ESWL: 2) and two (4.4%) in the placebo arm (URS: 1, ESWL: 1) required intervention before the end of the study. This difference was statistically non-significant (p=0.27). None of the patients treated with tamsulosin and three patients (6.7%) treated with placebo failed to expel their stone until day 21. The overall intervention rate was 13.3% in the tamsulosin and 8.9% in the placebo arm (p=0.74).

Four patients (8.9%) in the tamsulosin arm reported minor side effects. One patient discontinued therapy due to diarrhoea and subsequently was treated by ESWL. One patient with a mild cutaneous reaction and two patients with retrograde ejaculation continued therapy. In the placebo arm, one patient (2.2%) reported dizziness and inappetence but continued therapy.

Discussion

This first randomised, double-blind and placebo-controlled trial, investigating the efficacy of MET revealed that tamsulosin treatment did not improve the spontaneous expulsion rate of single distal ureteral stones ≤7mm. The proportion of patients experiencing stone expulsion within 21 days was even slightly, but not significantly lower in the tamsulosin arm than in the placebo arm. This finding is in contrast to the results of previous clinical trials which have reported significant improvements of the stone expulsion rate using tamsulosin [10-12, 15]. Two possible reasons have to be highlighted in this context: 1.) The actual stone size and 2.) The differences in study design between this and the previous trials.

Stone size has been identified as an important predictive factor for ureteral stone expulsion [20-22]. The probability for distal ureteral stones to pass spontaneously is as high as 71-98% for stones of 5mm or less and only 25-51% for stones greater than 5mm [20, 23, 24]. Approximately 80% of the stones in the present trial were 5mm or smaller. The actual stone size may be a reason for the high stone expulsion rate in the placebo arm. Yet, it remains unclear if the lack of improvement of the stone expulsion rate in the tamsulosin arm is attributable to the present stone size as well. The majority of stones in the trials reporting a beneficial effect of tamsulosin on the stone expulsion rate were greater than 5mm [10, 12, 15, 18]. It is reasonable to presume that the efficacy of MET will be relatively greater for larger stones, as smaller stones are more likely to pass without any treatment. However, currently it is not known whether a potential alpha-blocker effect on stone expulsion depends on ureteral stone size. In the present trial, patients with stones greater than 5mm had a lower chance to pass their stone spontaneously but tamsulosin treatment did not improve the expulsion rate of these stones. Admittedly, the study was not powered for this subgroup analysis and therefore the value of this analysis is limited.

Three meta-analyses have confirmed a positive effect of alpha-blocker therapy on the stone expulsion rate [25-27]. However, important potential confounders which may affect the

validity of the results and may lead to an over-estimation of the identified treatment effect have also been pointed out [25-28]. Although most of the published studies were randomised, reporting of randomisation methods was often unclear or even absent, as placebo-treatment and blinding to treatment were in general. Furthermore, determination of the stone status by abdominal CT at the end of the study was not performed in most of the previous studies. The differences in study design between the present and previous trials may therefore be an additional factor for the different outcomes. Interestingly, in accordance with the results of the present study, the only other double-blind, placebo-controlled study for alpha-blocker therapy of distal ureteral stones also revealed no improvement in the stone expulsion rate [29]. In this study, the mean stone size was smaller than 5mm as well but the non-subtype-selective alpha-1-receptor blocker alfuzosin was investigated.

The decision for a conservative medical or an active interventional treatment not only depends on the overall probability of stone expulsion. For many patients, factors like time to convalescence or re-exposure to dreaded colics during conservative treatment have a considerable impact on the decision to opt for an interventional treatment.

A faster and less painful stone expulsion, irrespective of stone size, has constantly been reported with MET [10, 13, 16]. In the present trial, median time to stone passage was three days shorter for patients treated with tamsulosin than for patients treated with placebo. However, although this difference may be clinically meaningful, it was statistically non-significant.

The secondary endpoint "total intake of analgesics", however, was significantly different between the treatment arms. Patients in the tamsulosin arm required fewer analgesics until stone expulsion than patients in the placebo arm. This difference may be attributable to the accelerated stone expulsion with a consecutive shorter time at risk for painful events. Additionally, a true analgesic effect of tamsulosin has also been reported [30]. The lower maximum pain scores in the tamsulosin arm already during the first days support the

existence of such an effect. Thus, pain modulation seems to be an important feature of MET with tamsulosin in patients with stones ≤ 7mm.

In both treatment arms no serious complications were recorded. Adverse events of tamsulosin treatment were mild and led to therapy discontinuation in one patient only.

Some limitations of the present trial deserve mention. The smaller stone size in the present trial compared to previous trials makes it difficult to directly compare the results of the different trials. Furthermore, for 32% of the patients the exact time of stone passage was not available. Thus, they needed to be censored at the last known date of stone presence. Therefore, the secondary end-point "time to stone passage" is based on Kaplan-Meier estimation.

Conclusion:

Patients with single, distal ureteral stones ≤ 7mm do not benefit from MET with tamsulosin in terms of an improved expulsion rate. Nevertheless, the generally well tolerated treatment may be beneficial for these patients due to an analgesic effect and thus a reduced need of analgesics until stone expulsion.

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Figure legends:

Figure 1: Trial profile

Figure 2: Kaplan Meier estimates for time to stone passage for the two treatment arms

Figure 3: Median maximum daily pain-score in the two treatment arms. The pain intensity was slightly higher in the placebo arm until day 4. After the fourth day of treatment the differences were marginal.

Table 1: Baseline characteristics of 45 patients treated with tamsulosin and 45 treated with placebo.

	Tamsulosin	Placebo	p-value
Age (years)	36 (30-44)	41 (33-54)	0.07
Sex			0.57
male	39 (86.7%)	36 (80%)	
female	6 (13.3%)	9 (20%)	
Stone size (mm)	4.1 (3.5-4.9)	3.8 (3.4-4.3)	0.3
Size distribution			0.43
< 5mm	34 (75.6%)	38 (84.4%)	
≥ 5mm	11 (24.4%)	7 (15.6%)	
Side			0.034*
left	18 (40%)	29 (64.4%)	
right	27 (60%)	16 (35.6%)	
Stone location			0.66
distal	27 (60%)	30 (66.7%)	
ureterovesical junction	18 (40%)	15 (33.3%)	

Data are presented as median (interquartile range) or number (proportion within treatment arm).
* indicates a significant difference between the treatment arms.

505 **Table 2**: Multiple Cox regression analysis for predictive factors for the secondary endpoint
506 "time to stone passage"
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Variables	p-value	Hazard ratio	95% confidence interval
Therapy	0.97	0.99	0.55 – 1.79
Stone Location	0.0005	3.17	1.66 – 6.05
Stone size	0.42	0.89	0.66 – 1.19

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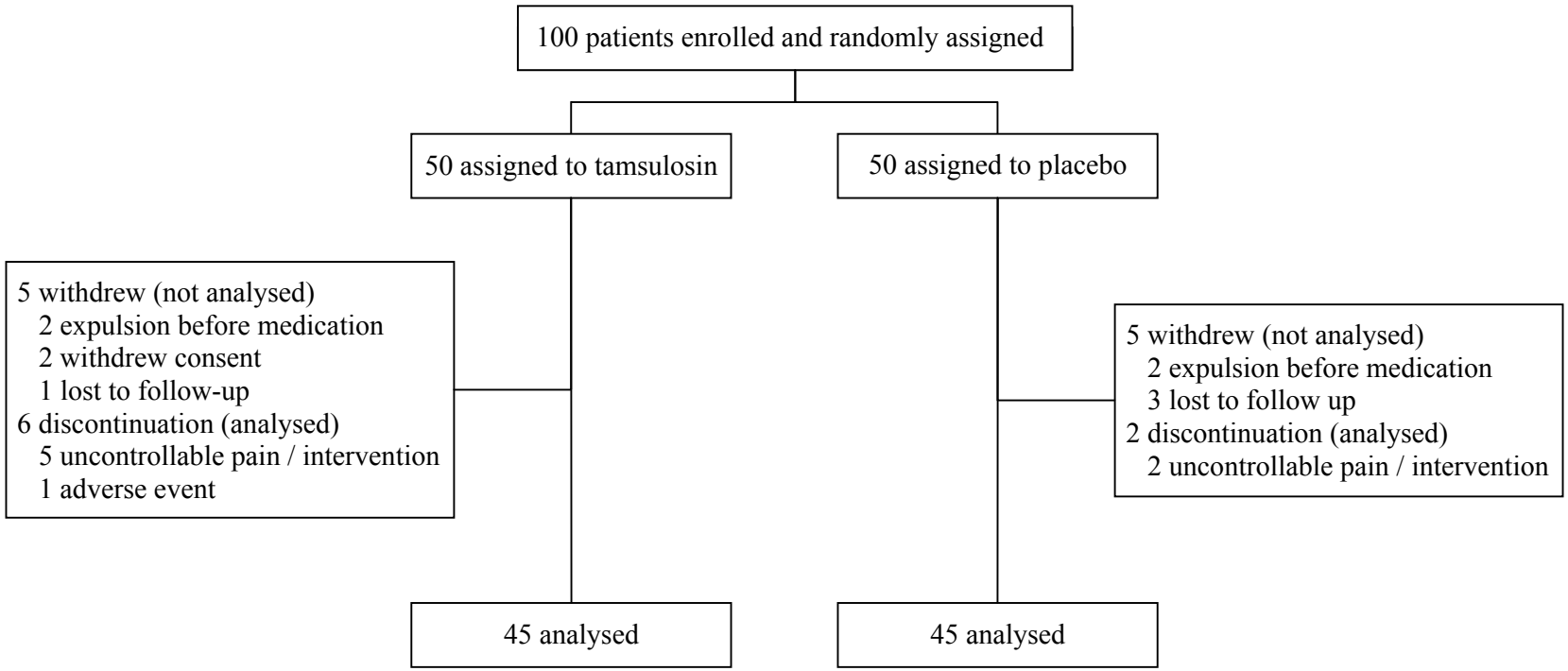
Illustration



Illustration

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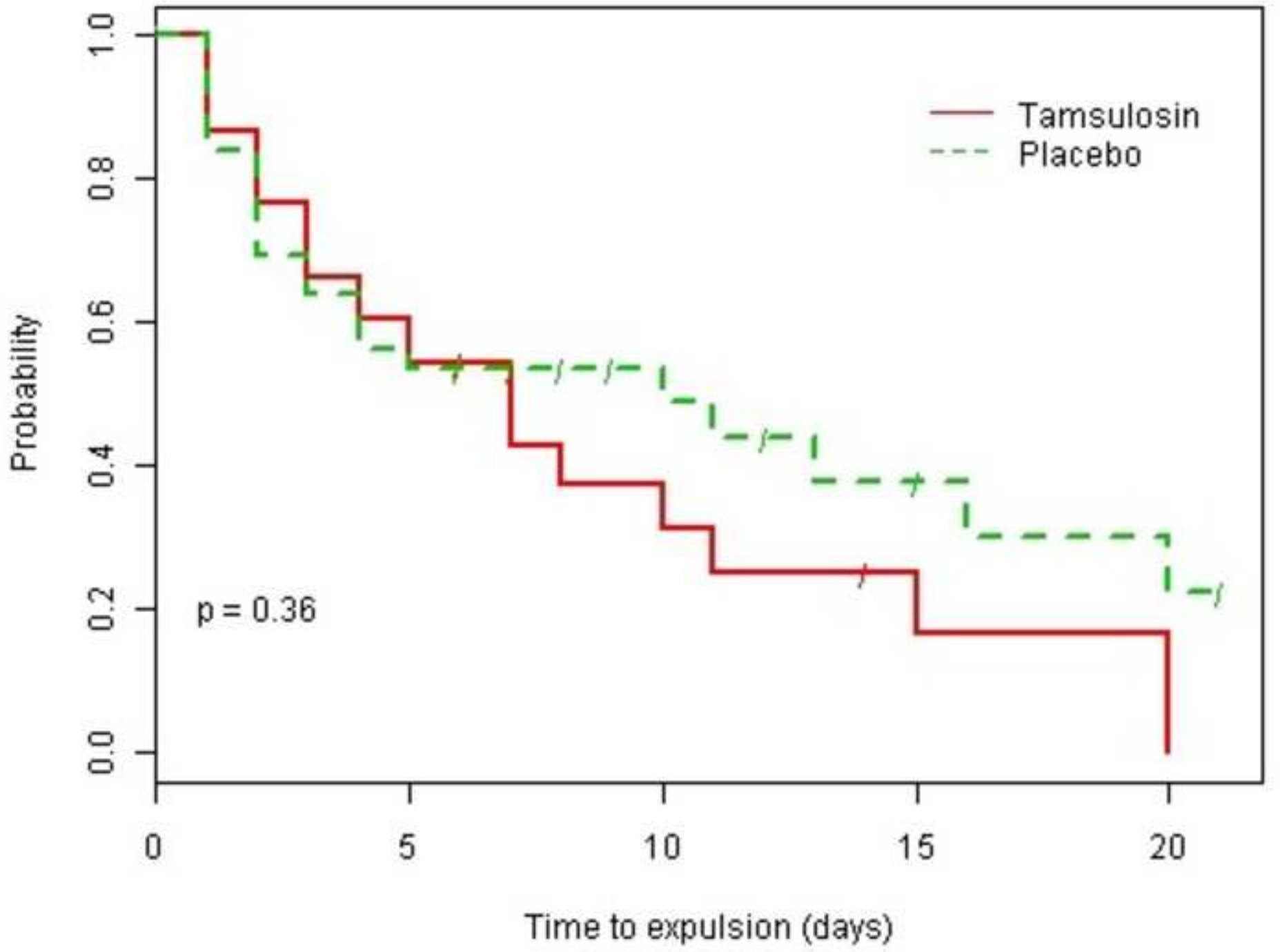

Illustration

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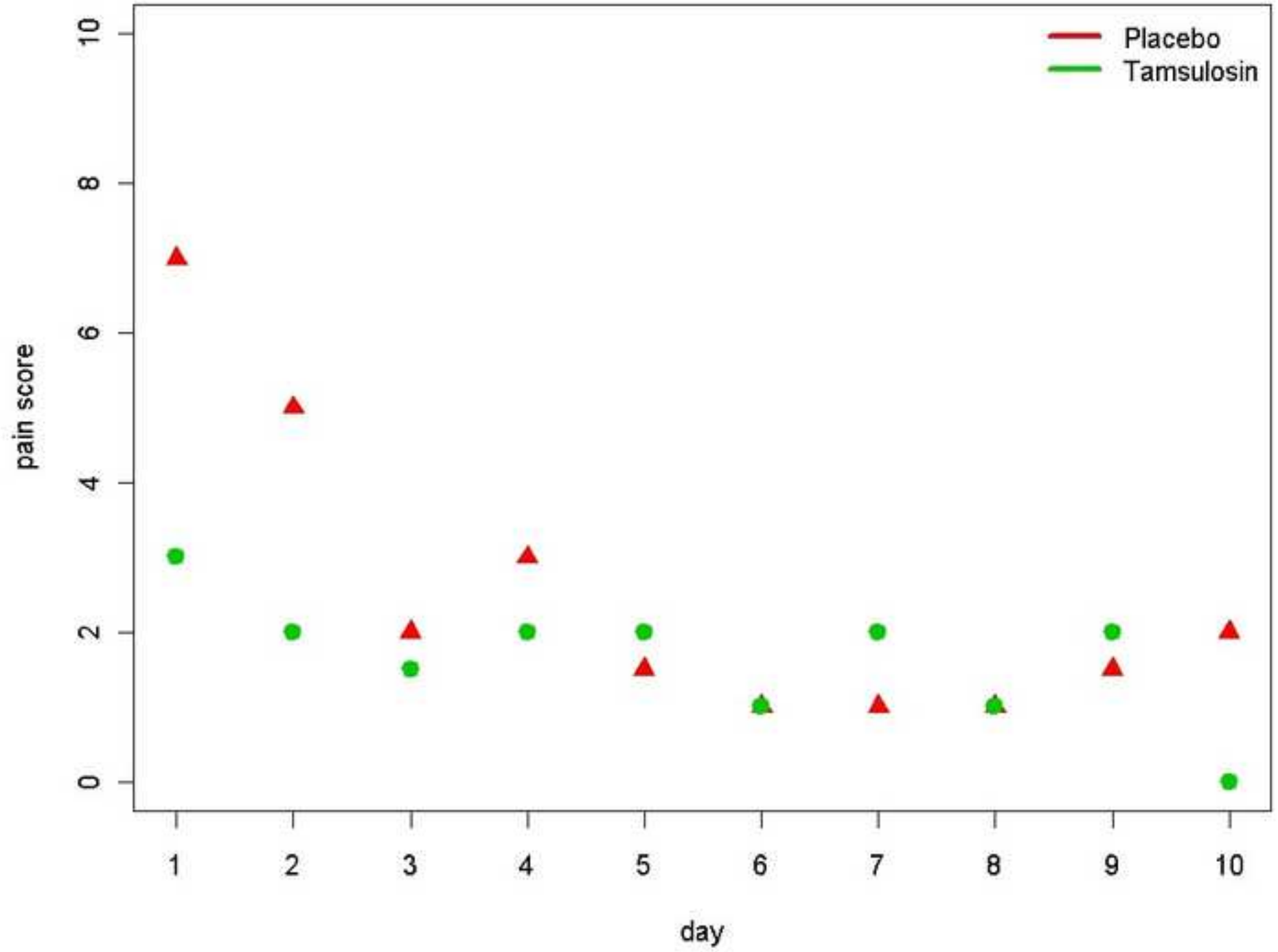

***Take Home Message**

TAKE HOME MESSAGE

Tamsulosin did not improve the stone expulsion rate of patients with single distal ureteral stones ≤ 7mm in this randomised, double-blind, placebo-controlled trial. Nonetheless, patients may benefit from a supportive analgesic effect with a reduced need for analgesics.